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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,217	02/01/2001	Brian S. Hilbush	98,430	9069

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,217	HILBUSH ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-63 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7,9,10,23-36,38 and 51-58 is/are rejected.

7)☒ Claim(s) 8,11-22,37,39-50 and 59-63 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 07/05/01 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in the Paper filed is acknowledged. With regard to the election of primers, Applicant correctly interpreted the election to require selection of enough primers to perform the method on one sample following the method claimed. Consequently, the primers elected by Applicant will be examined.

Information Disclosure Statement

2. The information disclosure statement filed July 5, 2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

The Sutcliffe reference was not submitted and was therefore not considered. The remaining references had been submitted in the parent application and were considered in that application.

Double Patenting

3. Claims 1-63 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 and 42-72 of copending Application No.09/186,869. Although the conflicting claims are not identical, they are not patentably distinct from each other because the current claims

are similar in scope and methodology to claims 3 and 4, in particular of copending Application No. 09/186,869.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-7, 9, 10, 24-31, 33-36, 38, 51-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693).

Erlander teaches an improved method for the simultaneous sequence-specific identification of mRNAs in a mRNA population comprising:

(a) preparing double-stranded cDNAs from an mRNA population optionally enriched for Poly A sequences (page 20, lines 8-13) using mixture of 12 anchor primers each anchor primer having a 5' and 3' terminus and including;

(i) phasing residues -V-N located at the 3' end of each of the anchor primers, wherein V is a deoxyribonucleotide selected from the group consisting of A, C, and G; and N is a deoxyribonucleotide selected from the group consisting of A, C, G, and T, the mixture including anchor primers containing all possibilities for V and N (page 8, lines 18-36),

(ii) a tract of from 7 to 40 T residues towards the 5' end relative to the phasing residues (see page 8, lines 18-36 and page 10, SEQ ID NO: 2, lines 24-26, for example),

(iii) a stuffer segment of from 4 to 40 nucleotides, the stuffer segment being located to the 5'-side of the site for cleavage by the restriction endonuclease (see page 8, lines 18-36),

(iv) a site for cleavage by a restriction endonuclease that recognizes more than six bases, the site for cleavage being located to the 5'-side of the tract of T residues which site would necessarily function as a segment complementary to a PCR primer,

(b) digesting the double stranded cDNA population with a two restriction endonucleases, one of which recognizes four nucleotide sequences outside the anchor primer (page 9, lines 1-11),

(d) ligating the double stranded cleaved cDNA from step (b) into an adaptor/vector in an orientation that is antisense with respect to a bacteriophage-specific promoter within the vector, (page 9, lines 1-11), expressly teaching the use of the pBC SK vector in which the NotI restriction site is more than 15 nucleotides in length from the transcription initiation site of either T3 or T7 RNA polymerase promoter (page 22, lines 16-26),

(e) generating a first strand amplification products by transcribing the cRNA using reverse transcriptase and by dividing the cRNA preparation into sixteen subpools and transcribing first-strand cDNA from each subpool, using a thermostable reverse transcriptase and one of sixteen primers whose 3'-terminus is -N-N, wherein N is one of the four deoxyribonucleotides A, C, G, or T, the primer being at least 15 nucleotides in length, corresponding in sequence to the 3'-end of the bacteriophage-specific promoter,

and extending across into at least the first two nucleotides of the cRNA, the mixture including all possibilities for the 3'-terminal two nucleotides; (page 9, lines 21-31),

(f) generating a second set of PCR products by using the product of transcription in each of the sixteen subpools as a template for a polymerase chain reaction with a 3'-primer that corresponds in sequence to a sequence in the vector adjoining the site of insertion of the cDNA sample in the vector and a 5'-primer selected from the group consisting of: (i) the primer from which first-strand cDNA was made for that subpool; (ii) the primer from which the first-strand cDNA was made for that subpool extended at its 3'-terminus by an additional residue -N, where N can be any of A, C, G, or T; and (iii) the primer used for the synthesis of first-strand cDNA for that subpool extended at its 3'-terminus by two additional residues -N-N, wherein N can be any of A, C, G, or T, to produce polymerase chain reaction amplified fragments; (page 9, line 32 to page 10, line 10),

(g) resolving the polymerase chain reaction amplified fragments which may be fluorescently labeled by electrophoresis to display bands representing the 3'-ends of mRNAs present in the sample (page 10, lines 11-13).

(h) characterizing each sequence specific PCR product by a partial sequence and length, thereby providing simultaneous sequence specific identification of multiple mRNA molecules in an RNA population (see page 33, lines 10-25).

With regard to claims 2 and 3, Erlander teaches generating a cRNA preparation of antisense cRNA transcripts by incubation of the linearized fragments with a bacteriophage-specific RNA polymerase capable of initiating transcription from the

bacteriophage-specific promoter (page 9, lines 16-20), and generating a first strand cDNA by transcribing the cRNA using reverse transcriptase and by dividing the cRNA preparation into sixteen subpools and transcribing first-strand cDNA from each subpool, using a thermostable reverse transcriptase and one of sixteen primers whose 3'-terminus is -N-N, wherein N is one of the four deoxyribonucleotides A, C, G, or T, the primer being at least 15 nucleotides in length followed by synthesizing the second DNA strand (see page 9, lines 21-31),

With regard to claim 4, Erlander teaches a site for cleavage by a restriction endonuclease that recognizes more than six bases, the site for cleavage being located to the 5'-side of the tract of T residues (see page 8, lines 18-36).

With regard to claim 5, Erlander teaches and suggests lengthing the number of Ns, to result, for example, in V-N-N (see page 27, lines 1-5).

With regard to claim 6, Erlander exemplifies the situation where X and Y are 1 (see page 9, lines 21-31).

With regard to claim 7, Erlander teaches 18 T nucleotides (see page 47, claim 2).

With regard to claims 9 and 10, Erlander teaches the use of the T3 promoter (page 24, lines 16-27).

With regard to the specific restriction enzymes chosen in claims 24-29, Erlander teaches the use of EcoRI, Not I and TaqI (see page 48, claims 11-14) as well as MspI (see page 50, line 13).

Erander does not teach interposing a step (here step (c)) of capture using biotin and streptavidin for the cDNA prior to amplification in order to avoid the necessity for cloning the sequence.

Kato teaches interposing a capture step using biotin labels and streptavidin coated magnetic beads for capture of labeled nucleic acid indexing amplified molecules prior to the amplification step (figure 1 and page 4, lines 30-40), which also addresses the limitations of claims 30 and 31.

Rothberg teaches additional motivations to use the capture method in DNA classification methods, including methods using phasing primers such as the method of Erlander (columne 32 and column 66). In particular, Rothberg notes that when primers are labeled with biotin, the resultant fragments can be more sensitively detected, stating "Such purified fragments can thereby be detected with increased sensitivity (see column 32, lines 32-33)." Rothberg also notes that amplification bias is reduced by capture which reduces the number of cycles necessary to achieve a desired signal to noise ratio in the analytical assay (see column 32, lines 53-58). Rothberg further teaches the association of cDNA synthesis with phasing primers where a PCR sequence is placed in the 5' end of the phasing primer as well as the subsequent capture of the amplification product using the biotin streptavidin system (see column 66, lines 14-30)

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to interposing a capture step using biotin labels and streptavidin coated magnetic beads for capture of labeled nucleic acid indexing amplified molecules in order to separate the nucleic acid products as taught by Kato in the method of Erlander since Kato states "By using a class-II restriction enzyme, a class IIS restriction enzyme and 64 biotinylated adaptors in the operations described above, the DNA or cDNA fragments generated by class II and class IIs restriction enzymes can

be separated. (Page 5, lines 53-55)." Further motivation is provided by Rothberg, who notes that when primers are labeled with biotin, the resultant fragments can be more sensitively detected, stating "Such purified fragments can thereby be detected with increased sensitivity (see column 32, lines 32-33)." An ordinary practitioner would have been motivated to use the biotin streptavidin system for isolation of nucleic acids in order to easily separate the components using magnetic beads as taught by Kato and Rothberg and in particular, to easily separate out the restricted DNA as taught by Kato and to reduce amplification bias and improve sensitivity as taught by Rothberg.

8. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) and further in view of Noronha et al (PCR Methods Appl (1992) 2:131-136).

Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) teaches the limitations of claims 1-7, 9, 10, 24-31, 33-36, 38, 51-57 as discussed above. Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) do not teach the use of phosphorothioate linkages.

Noronha teaches the use of phosphorothioate linkages in PCR in order to prevent primer degradation (abstract).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize phosphorothioate linkages as taught by Noronha in the method of Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) since Noronha

states "The data presented here demonstrate that while 3'-5' exonuclease activity can be a hindrance to efficient specific DNA amplification, its activity can be diverted from amplimer degradation and restricted to proofreading through the use of 3' sulfurized amplification amplimers (page 135, column 3)". An ordinary practitioner would have been motivated to combine the use of phosphorothioate oligonucleotides with the method of Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) in order to reduce background and amplimer degradation.

9. Claim 32 is rejected under 35 U.S.C. 103(a) as being unpatentable over Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) and further in view of Kris et al (U.S. Patent 6,238,869).

Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) teaches the limitations of claims 1-7, 9, 10, 24-31, 33-36, 38, 51-57 as discussed above. Erlander et al (WO 95/13369) in view of Kato et al (EP 735 144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) do not teach the use of n-oxysuccinimide esters to link components to the magnetic beads

Kris teaches the use of n-oxysuccinimide esters to link components to the magnetic beads (see column 23, lines 50-67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize n-oxysuccinimide esters as linkers as taught by Kris et al in the method of Erlander et al (WO 95/13369) in view of Kato et al (EP 735

144 A1) and further in view of Rothberg et al (U.S. Patent 5,972,693) since Kris notes that these are standard and equivalent modes of attachment in the art. As MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

Allowable Subject Matter

10. Claims 8, 11-22, 37, 39-50 and 59-63 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone numbers

for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634

June 13, 2003